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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,141	RAO ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 8/31/2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-14 are currently pending and are the subject of this Office Action. Claim 11 recites non-elected subject matter and is withdrawn from consideration.

Specification

The abstract of the disclosure is objected to because it contains over 150 words. Correction is required. See MPEP § 608.01(b).

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 9/7/2006 and 9/8/2006 were filed after the mailing date of the Non-Final Office Action on 6/1/2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-10 and 12-14 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, claims 1 and 14 recite "dual norepinephrine serotonin reuptake inhibitor[s]" or "triple reuptake inhibitor[s]" and claim 10 recites "an amino cyclopropane derivative." There is inadequate written description for these compounds.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

The specification does not describe a sufficient number of species as to convey possession of the entire genus encompassed by "dual norepinephrine serotonin reuptake inhibitor[s]", "triple reuptake inhibitor[s]" or "aminocyclopropane derivatives." Page 11, lines 14-16 of the specification defines an aminocyclopropane derivative as an aminocyclopropane

compound possessing suitable selective norepinephrine (NE)-serotonin (5-HT) reuptake inhibition. Suitable aminocyclopropane derivatives are disclosed in several patents and publications. However, there is no written description with respect to the structural features that characterize this broad genus of compounds. Further, applicants have provided no guidance on how one skilled in the art would make these compounds.

Pages 10-13 describe *preferred* dual norepinephrine serotonin reuptake inhibitors and triple reuptake inhibitors and incorporates essential subject matter (*e.g.* methods of determining NE:5-HT reuptake inhibition, methods of synthesizing compounds, etc,) by reference to other publications. However, the incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Applicants have not provided any means for the skilled artisan to determine exactly what compounds are "dual norepinephrine serotonin reuptake inhibitor[s]" or "triple reuptake inhibitor[s]" aside from the explicitly named compounds (*e.g.* milnacipran, sibutramine, bicifadine, venlaxafine, etc.) (pages 10-13). The only distinguishing characteristic present is that an agent inhibits norepinephrine and serotonin. There is no description of structural characteristics that are required to retain such biological activity. Accordingly, in the absence of

sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claims 1-10 and 12-14 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating DSP, does not reasonably provide enablement for the total prevention of DSP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In the instant case, the claims are drawn to both the treatment of and the prevention of depression secondary to pain. Although the specification provides support for and enables the treatment of DSP using the claimed NSRI compounds by means of diagnosis, dosing, administration routes, etc., it does not provide adequate enablement for the total prevention of DSP. It is not clear from the specification how one skilled in the art would use the claimed methods for the prevention of depression secondary to pain. For example, the specification does not provide any guidance on how one skilled in the art would evaluate a patient to determine if they may develop DSP and might therefore need prevention therapy, as many patients with pain may never develop depression and would therefore not need prevention therapy. Further, it would require years of undue experimentation, with no reasonable expectation of success, to test whether treatment with an NSRI could absolutely prevent depression secondary to pain.

To enable the prevention of any disorder there would have to be some teaching or suggestion in the prior art that said disorder can be prevented. In the case of general depression, let alone a specific type of depression, there is no such teaching. As such, the Office would

require specific enablement with respect to the diagnosis of a patient population susceptible to DSP as well as methods of treating said patient population for years to demonstrate that the treated group never develops DSP (*i.e.* DSP has been prevented). The instant specification provides no such enablement.

In view of the above, the specification does not provide enablement for the absolute prevention of depression secondary to pain by administering an NSRI because it would take years of undue experimentation for the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7 and 12-13 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996).

Applicant's arguments filed 8/31/2006 have been fully considered but they are not persuasive. Applicants argue, *inter alia*, that Ruoff *et al.* teach away from the claimed methods because the reference discloses that the norepinephrine serotonin reuptake inhibitor (NSRI), venlafaxine, is associated with serious side effects. As such, applicants assert that one skilled in the art would not be motivated to administer a NSRI to treat depression secondary to pain (DSP). This argument is not persuasive. Examiner respectively submits that the prior art: 1) teaches all of the claimed limitations; 2) provides ample motivation to combine Mouzin *et al.*, Moret *et al.* (1985) and Ruoff (1996); and 3) provides the skilled artisan with at least a reasonable expectation of success. The fact that venlafaxine is associated with side effects does not teach

away from the claimed methods. This is only one example of an NSRI that happens to be associated with side effects. For example, the NSRI milnacipran has been used to treat depression for years with minimal side effects.

Mouzin *et al.* ('836 patent) disclose that milnacipran, salts of milnacipran, and derivatives thereof are useful in the treatment of depression (see especially Abstract).

Moret *et al.* disclose that milnacipran is a dual norepinephrine (NE) serotonin (5-HT) reuptake inhibitor (see especially Abstract), has a NE:5-HT reuptake inhibition ratio of 2:1 (Table 4, page 1215), and can be used to treat depression at a dose of 50 mg twice a day (page 1218, last paragraph).

Thus, Mouzin and Moret provide motivation to treat depression with the NSRI, milnacipran. Neither Mouzin *et al.* nor Moret *et al.* specifically teach the treatment of DSP with a NSRI.

However, Ruoff discloses that the neurotransmitters serotonin and norepinephrine have been implicated in both perception of pain and the pathogenesis of depression and that antidepressants have been shown to be effective in the treatment of a variety of chronic pain syndromes, including peripheral neuropathic pain, headache, migraine, facial pain, fibrosis, and rheumatic pain (page S27). The reference further states that, "Regardless of whether depression is secondary to the pain syndrome or is the primary condition, the mood disorder should be thoroughly assessed and treated pharmacologically" (page S28, "Treatment Approaches"). Ruoff further discloses that the NSRI antidepressant, venlafaxine, exerts its antidepressant activity through selective inhibition of norepinephrine and serotonin uptake (Page S30, "Venlafaxine").

Thus, the reference provides further motivation to treat depression with a NSRI.

As noted by the Applicants, the relationship between chronic pain and depression is complex and not entirely understood. However, the treatment of depression secondary to pain is suggested by the reference to be the same as that for treatment of other types of depression. Ruoff states on Page S32, last paragraph that:

> "Clinicians must carefully assess patients prior to initiating antidepressant therapy. However, once depression is diagnosed, treatment in the patient with chronic pain is no different than in patients without pain. Antidepressant therapy should be started early and in full doses."

Clearly, this statement, and in fact the entire disclosure of Ruoff, provides ample motivation to treat DSP with NSRIs. Ruoff explicitly states that the treatment of depression in patients with chronic pain (*i.e.* depression secondary to pain) is no different than treating other types of depression. As such, the skilled artisan would have been motivated to treat DSP with known antidepressants, including the NSRI taught by Mouzin and Moret.

Examiner respectfully maintains that the instantly claimed methods of treating DSP with NSRIs would have been *prima facie* obvious given the known use of the NSRI milnacipran to treat depression. In addition, the prior art is clear with regard to the relationship between pain and depression; as Applicants have previously stated in their arguments, the relationship is complex and not entirely understood. However, it is the *diagnosis of depression* in patients having chronic pain that is complex. Once that diagnosis has been properly made, the treatment is, as suggested by Ruoff, no different than that used for depression without pain. In fact, at the

time the invention was made, the prior art made no distinction in the treatment of depression and atypical depression secondary to pain.

Thus, Claims 1-7 and 12-13 would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art. This is especially true given that milnacipran was known in the art to be a dual norepinephrine serotonin uptake inhibitor useful in the treatment of depression due to its minimal side effects. The drug had been used, in the doses instantly claimed, to treat major depression (Moret *et al.*, page 1218). Lastly, Ruoff explicitly states that the treatment of depression in a patient having chronic pain is no different than in patients without pain. As such, the skilled artisan would be motivated to treat DSP with any antidepressant, including the NSRI milnacipran as taught by Mouzin *et al.* and Moret *et al.* and would have been imbued with at least a reasonable expectation that such treatment would be effective.

Claim 8 is again rejected under 35 U.S.C. § 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996) as applied to claims 1-7 and 12-13 above, and further in view of Shuto *et al.* (J. Med. Chem., 1995, 38:2964-2968).

Applicant's arguments filed 8/31/2006 have been fully considered but they are not persuasive. As discussed *supra*, applicant's arguments are not persuasive regarding the Mouzin, Moret, and Ruoff references. As such, because no new arguments were introduced with respect to the Shuto *et al.* reference, the instant rejection is maintained for the reasons set forth in the Office Action mailed 6/1/2006.

Mouzin, Moret, and Ruoff teach as above.

Shuto *et al.* disclose that milnacipran, a clinically used antidepressant, is an effective NMDA receptor antagonist (Table 1, Page 2966). The ability of milnacipran, a dual serotonin norepinephrine inhibitor, to antagonize NMDA receptors is an inherent property of the drug as evidenced by Shuto *et al.* and is therefore rendered obvious by the combined references.

Thus, the method of Claim 8 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 9 is again rejected under 35 U.S.C. § 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996) as applied to claims 1-7 and 12-13 above, and further in view of Puech *et al.* (Int. J. Psychopharm., 1997, 12:99-108).

Applicant's arguments filed 8/31/2006 have been fully considered but they are not persuasive. As discussed *supra*, applicant's arguments are not persuasive regarding the Mouzin, Moret, and Ruoff references. As such, because no new arguments were introduced with respect to the Puech *et al.* reference, the instant rejection is maintained for the reasons set forth in the Office Action mailed 6/1/2006.

Mouzin, Moret, and Ruoff teach as above.

Puech *et al.* disclose that milnacipran, a new serotonin and noradrenaline (synonymous with norepinephrine) reuptake inhibitor, has comparable or superior antidepressant effects to tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) without the side effects of TCAs (see especially Abstract). There have been no reported increases in seizures

associated with milnacipran in the over 4000 patients who have received the drug in therapeutic trials (Page 104, "Tolerability and Safety"). Table V (page 105) of the reference compares the adverse events associated with milnacipran (50 mg twice a day), TCAs, and SSRIs.

Thus, the method of Claim 9 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Claims 1-10 and 12-14 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

September 18, 2006

9/28/06
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SUPERVISORY PATENT EXAMINER